114 (100), 97 (29.7), 83 (15.9), 72 (16.3), 57 (52.0), 41 (60.1), 29 (38.8); high-resolution mass spectrum, *m/e* 242.1266 (calcd for $C_{11}H_{18}N_2O_4$, 242.1265).

***N*-Butyl-4-oxo-3-aza-8-oxabicyclo[3.2.1]octane-*exo*-2-carboxamide (5c).** Compound **5b** (307 mg, 1.27 mmol) was dissolved in methanol (6 mL). Water (4.3 mL) and sodium acetate (1.27 g) were added to the solution. The solution was stirred at room temperature under nitrogen while 1.96 mL of 20% $TiCl_3$ in water was added dropwise via syringe. After the addition was completed, the solution was stirred for 15 min. Then the solution was poured into 20 mL of water, and a few drops of concentrated hydrochloric acid was added to the solution. The solution was extracted with six 10-mL portions of ethyl acetate. The combined organic layers were washed with aqueous 5% sodium carbonate and dried with anhydrous sodium sulfate. The solvent was evaporated in vacuo. The solid was separated by column chromatography (chloroform/methanol, 9:1) on silica gel (5.0 g). It gave 104 mg (36.2%) of **5c**: R_f 0.20 (chloroform/methanol, 9:1); mp 177–178 °C (benzene); IR ($CHCl_3$) 3450, 3410, 3010, 2975, 2950, 2890, 1695, 1690, 1535, 1475, 1455, 1345, 1290, 1030, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, J = 6.4 Hz, 3 H), 1.20–1.70 (m, 4 H), 2.00–2.35 (m, 4 H), 3.33 (q, J = 6 Hz, 2 H), 3.68 (d, J = 3.4 Hz, 1 H), 4.50 (m, 1 H), 4.91 (d, J = 5 Hz, 1 H), 7.00–7.40 (m, 2 H); MS, *m/e* (relative intensity) 226 (3.8), 184 (9.2), 155 (2.9), 127 (100), 109 (34.8), 98 (59.9), 81 (7.2), 70 (13.2), 57 (13.8), 43 (22.5), 30 (22.0); high-resolution mass spectrum, *m/e* 226.1328 (calcd for $C_{11}H_{18}N_2O_3$, 226.1316).

Solvolysis of 2c. Compound **2c** (119 mg, 0.713 mmol) was dissolved in 5 mL of 6 N hydrochloric acid. The solution was refluxed for 36 h. The solvent was removed under reduced pressure. After addition of methanol (5 mL), the solvent was evaporated at 50 °C, and this procedure was repeated 5 times. The residue (137 mg) was separated by silica gel (6 g) column chromatography (chloroform/methanol, 9:1). Product **2d** (monohydrate, 73.3 mg, 40.5%) was yielded: R_f 0.10 (chloroform/methanol, 9:1); mp 171–172 °C (benzene); IR ($CHCl_3$) 3600–3300, 2950, 1735, 1620, 1520, 1445, 1395, 1305, 1170, 990 cm^{-1}; ^1H NMR (CD_3OD) δ 0.89 (s, 3 H), 1.01 (s, 3 H), 1.34 (s, 3 H), 1.40–1.53 (m, 1 H), 1.78–1.89 (m, 1 H), 1.95–2.07 (m, 2 H), 2.16–2.30 (m, 2 H), 2.46 (d, J = 11 Hz, 1 H), 3.66 (s, 3 H); ^{13}C NMR (CD_3OD) δ 18.3 (q), 21.5 (q), 23.1 (q), 27.2 (t), 35.6 (t), 36.1 (t), 44.5 (d), 45.9 (s), 52.2 (q), 65.8 (s), 175.1 (s). Anal. Calcd for $C_{11}H_{21}NO_2 \cdot HCl \cdot H_2O$: C, 52.06; H, 9.53; N, 5.52. Found: C, 51.69; H, 9.33; N, 5.50.

Solvolysis of 3c. Compound **3c** (184 mg, 0.915 mmol) was dissolved in 6 mL of 2 N hydrochloric acid, and the solution was refluxed for 4 h. The water was evaporated, and 5 mL of methanol was added. The solution was refluxed for 1 h and concentrated. The residue (259 mg) was separated by alumina (10 g, Wako, 200 mesh) column chromatography (chloroform/methanol, 4:1). Product **3d** (191 mg (89.6%)) was obtained: R_f 0.25 (chloroform/methanol, 4:1); IR (CCl_4) 3400–3300, 1740, 1600, 1520, 1440, 1365, 1200, 1160, 700 cm^{-1}; ^1H NMR (CCl_4) δ 1.20–2.20 (m, 9 H), 2.45–2.90 (m, 1 H), 3.67 (s, 3 H), 3.65 (m, 1 H), 7.20 (s, 5 H); MS, *m/e* (rel intensity) 233 (0.8), 201 (21.6), 173 (4.3), 160 (10.1), 41 (10.8), 28 (10.3); high-resolution mass spectrum, *m/e* 233.1420 (calcd for $C_{14}H_{19}NO_2$, 233.1414).

Lactamization of 3d. Compound **3d** (191 mg, 0.820 mmol) was dissolved in 1.0 mL of benzene, and the solution was refluxed for 15 min. The solution was concentrated in vacuo, and the residue (244 mg) was separated by silica gel (4 g) column chromatography (chloroform/methanol), 9:1). The separation gave **3c** (146 mg, 88.6%); mp 159–160 °C. The spectra were identical with those of authentic **3c**.

^1H NMR Study of the Photoproducts. To determine the stereochemistry of the product, the following experiments were attempted. 3-Nitro-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid was reacemized by addition of aqueous sodium hydroxide (at pH 11.5, *exo*-4-carboxyl:*endo*-4-carboxyl = 71:29, from ^1H NMR). After methyl esterification of it with diazomethane, the ester was irradiated in ammonia/methanol. The separation of the products gave a hydroxamic acid (4-epimerized, 3-hydroxy-4-(methoxycarbonyl)-3-aza-8-oxabicyclo[3.2.1]octan-2-one): ^1H NMR ($CDCl_3$) δ 1.90–2.30 (m, 4 H), 3.25 (s, 0.24 H), 3.83 (s, 3 H), 4.06 (s, 0.76 H), 4.50–4.60 (m, 1 H), 4.70–4.90 (m, 1 H), 7.00–8.00 (broad, 1 H); IR ($CHCl_3$) 3350 (broad), 1740, 1640 cm^{-1}; high-resolution mass spectrum, *m/e* 201.0597 (calcd for $C_8H_{11}NO_2$, 201.0559). From ^1H NMR study, the ratio of the diastereomer was determined (*exo*-4-(methoxycarbonyl) (4-equatorial hydrogen):*endo*-4-(methoxycarbonyl) (4-axial hydrogen) = 76:24). In the same way, from the racemized acid, **5b** was made (^1H NMR of H-C(4) δ 3.25 (s, 0.29 H, axial hydrogen), 3.70 (d, J = 3.4 Hz, 0.71 H, equatorial hydrogen). So we can decide the ratio of the diastereomers of the hydroxamic acids. Actually none of the products (in Table I) had any axial hydrogen at C(4).

Acknowledgment. We are grateful to Prof. Werner Herz (Florida State University) for kindly correcting our English. Thanks are also given to the referees for their helpful advice. We thank the fund of Mitsui Petrochemical Industries, Ltd., for a fellowship (K.K.).

Synthesis and Characterization of a Novel Calix[4]arene Tetramethyl Tetraether

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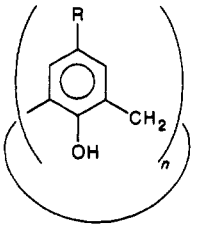
Calixarenes **1** are [1.*n*]metacyclophanes comprising cyclic arrays of phenolic residues attached by methylene units at the positions ortho to the hydroxy groups.[1] These



1, *n* = 4-8

materials have the ability to entrap other molecules within their central cavities. Thus, they are attractive models for mimicking enzyme–substrate interactions.[2] Structures with both inward- and outward-turned functional groups have been the object of synthetic efforts. The hydroxy inward-turned calix[4]arenes (cyclic tetramers) have been obtained either by base-induced condensation of *p*-alkylphenols with formaldehyde[3] or by stepwise syntheses.[1] The calix[4]arenes with outward-turned hydroxy groups have been synthesized by acid-catalyzed condensation of resorcinol with various aldehydes[4] and by the reaction of a bisphenol with paraformaldehyde.[5] Herein, we report an efficient synthesis of 6,10,18,22-tetramethoxy-4,12,16,24,25,26,27,28-octamethylpentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene (**2**) via a Lewis acid mediated tetramerization of a *p*-methoxybenzyl alcohol. This transformation reproducibly gives with selectivity a cyclic tetramer, in 80% yield, with methoxy groups adorning the outside periphery.

A solution of the known 2,6-dimethyl-4-methoxybenzyl alcohol[6] in dichloromethane was treated with 0.6 equiv of anhydrous aluminum chloride in five portions over a period of 2 h. As the reaction proceeded, the solution turned dark

(1) Gutsche, C. D.; No, K. H. *J. Org. Chem.* **1982**, *47*, 2708–2712; *Ibid.* **1982**, *47*, 2713.
(2) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161.
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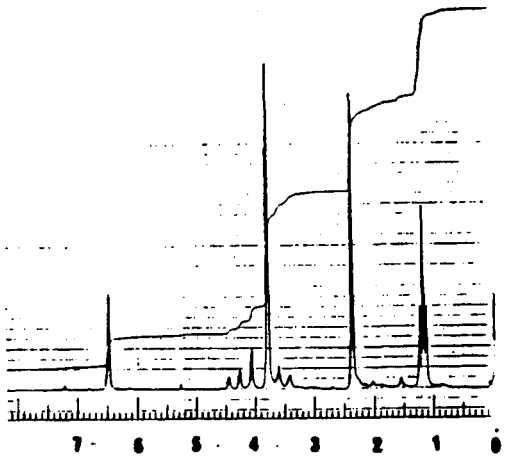
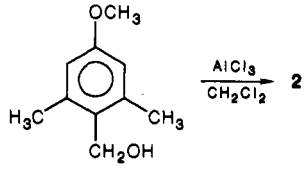
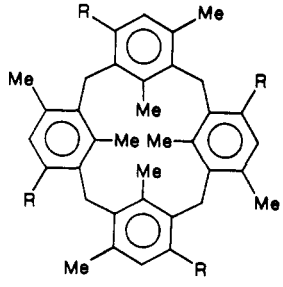


Figure 1. ^{1}H NMR (90 MHz) spectrum of calix[4]arene 2.

blue in color. Water was added to quench unreacted aluminum chloride. Partitioning of the aqueous mixture with dichloromethane gave the crude product as a white powder after solvent removal. The crude product was shown by HPLC (Waters' M Bondapak C-18 column, 30 cm × 3.9 mm i.d.; mobile phase, 100% CH_3CN; flow rate, 1.5 mL/min) to consist of a single major component (retention time 8 min) of 90% purity. The purity of the crude product was also reflected by the ^{1}H NMR spectrum, which was nearly identical with that of the product after purification by chromatography (silica gel) and recrystallization. Both ^{1}H NMR and ^{13}C NMR are in agreement with the structure 2. Both low- and high-resolution mass



spectral analysis showed it to be a cyclic tetramer (M^+ 592). The parent ion peak was also the base peak with the second most intense peak at m/e 149 (relative intensity, 56). Scanning up to 1500 and a probe temperature up to 500 °C revealed no higher cyclic oligomers, e.g., hexamer (M^+ 888), octamer (M^+ 1184), or homooxacalix[4]arene. The elemental analysis is consistent with the assigned structure with incorporation of 0.5 equiv of H_2O.



2, R = OMe
3, R = Me

^{1}H NMR (100 MHz) spectrum of 2 (Figure 1) is different from that of the known metacyclophane 3 (Figure 2) obtained from reaction of chloromethylmesitylene and stannic chloride,[7] which has been shown to exist in a 1,3-alternate-like conformation.[8] The major difference in the

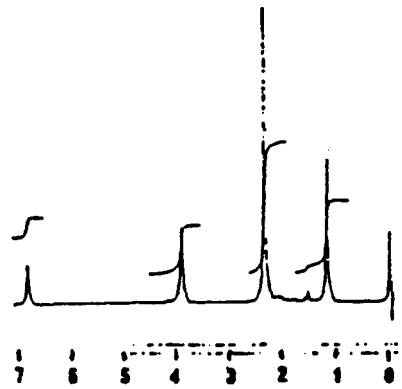


Figure 2. ^{1}H NMR (60 MHz) spectrum of metacyclophane 3.

^{1}H NMR of 2 and 3 lies in the signals reflecting the methylene protons and the four methyls in the ring. The methylene protons of 2 exhibited two doublets and two singlets (one obscured by the methoxy signals), indicating four different environments for eight methylene protons. This methylene proton pattern falls into the category of the "six-line pattern" which is consistent with a partial cone conformation as pointed out by Gutsche[9] et al. for this type of compound. The three prominent singlets in the ratio of 1:2:1 in the upfield region of the spectrum for the four methyl groups inside the ring are compatible only with a partial cone conformation.[8] The exceptional upfield shift for the four methyl groups inside the ring at δ 1.12 to 1.23 is the result of being strongly shielded by the aryl ring current. The temperature variation ^{1}H NMR spectra indicates that 2 is conformationally rigid at temperatures up to 160 °C.

To our knowledge, this synthesis is the first example of *p*-alkoxybenzyl alcohol tetramerization in formation of a calix[4]arene. Our work in defining the scope and limitation of this type of transformation is in progress.

Experimental Section

Elemental analyses were performed at Galbraith Laboratories, Inc., Knoxville, TN. Melting points were obtained on a Mel-Temp apparatus and are uncorrected. The ^{1}H NMR (250 MHz) spectrum was obtained on a Bruker WM-250. The ^{1}H NMR (60 MHz) was obtained on a Varian EM-360 spectrometer. ^{1}H NMR (90 MHz) and ^{13}C NMR were obtained at 22.5 MHz on a JEOL FX-90/2. All the chemical shifts are reported on ppm downfield from internal tetramethylsilane. A Perkin-Elmer Model 197 spectrometer was used for infrared spectra. The mass spectra were obtained from Research Triangle Institute, Research Triangle Park, NC.

Preparation of 6,10,18,22-Tetramethoxy-4,12,16,24,25,26,27,28-octamethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (2). To a stirred solution of 1.0 g (6.0 mmol) of 2,6-dimethyl-4-methoxybenzyl alcohol in 50 mL of CH_2Cl_2 was added 0.5 g (3.75 mmol) of anhydrous $AlCl_3$ in five portions over 2 h. The TLC analysis indicated complete disappearance of the starting material. The mixture was diluted with 50 mL of CH_2Cl_2, followed by addition of 100 mL of H_2O to quench the unreacted $AlCl_3$. The resulting mixture was stirred for 10 min. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with a $NaHCO_3$ aqueous solution and water three times. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give 1.0 g of a white solid: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.08 (s, 3 H), 1.12 (s, 6 H), 1.20 (s, 3 H), 2.32 (s, 12 H), 3.33 and 3.58 (d, J = 16 Hz, 2 H), 3.80 (s, 12 H), 4.00 (s, 2 H), 4.18 and

(7) Bottino, F.; Montaudo, G.; Maravigna, P. *Ann. Chim. (Rome)* **1967**, *57*, 972. In our experiment, the reaction was carried out at 50 °C for 2 h to give 3 in 70% yield after recrystallization. When the identical conditions were applied to 2,6-dimethyl-4-methoxybenzyl alcohol, no formation of the calix[4]arene 2 was observed.

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4.45 (d, J = 16 Hz, 2 H), 6.40 (s, 4 H). The crude product (100 mg) was purified by preparative TLC (silica gel, 2 × 200 μM thickness) using 50% CH_2Cl_2 in hexane to give 80 mg (80% recovery) of the desired calix[4]arene as white solid (R_f 0.55): mp 335–365 °C (CH_2Cl_2); ^1H NMR ($CDCl_3$, 60 MHz) identical with the above data; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.12 (s, 3 H), 1.17 (s, 3 H), 1.18 (s, 3 H), 1.23 (s, 3 H), 2.36 (s, 6 H), 2.37 (s, 3 H), 3.52 (d, 1 H, J = 16.63 Hz), 3.58 (d, 1 H, J = 16.66 Hz), 3.78 (s, 3 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.81 (s, 2 H), 4.06 (s, 2 H), 4.34 (d, 1 H, J = 16.66 Hz), 4.36 (d, 1 H, J = 16.63 Hz,), 6.48 (s, 3 H), 6.49 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.39 (10%, CH_3), 16.90 (30%, 2 × CH_3), 17.25 (12%, CH_3), 21.89 (47%, 4 × CH_3), 26.25 (19%, $ArCH_2Ar$), 30.77 (9%, $ArCH_2Ar$), 55.58 (34%, OCH_3), 55.75 (20%, OCH_3), 109.95 (21%, Ar), 110.06 (15%, Ar), 110.14 (17%, Ar), 127.53 (16%, Ar), 127.66 (17%, Ar), 127.77 (13%, Ar), 132.16 (28%, Ar), 133.40 (6%, Ar), 133.46 (9%, Ar), 133.54 (9%, Ar), 133.62 (11%, Ar), 133.68 (12%, Ar), 133.81 (15%, Ar), 133.92 (9%, Ar), 137.36 (10%, Ar), 137.49 (22%, Ar), 137.68 (10%, Ar), 154.40 (13%, Ar), 154.51 (12%, Ar), 154.59 (11%, Ar), 154.70 (14%, Ar), 154.78 (8%, Ar); high-resolution mass spectrum calcd for $C_{40}H_{48}O_4$ 592.3552, found 592.3554. Anal. (dried in vacuo at 100 °C for 30 min prior to analysis). Calcd for $C_{40}H_{48}O_4 \cdot {}^1/_2H_2O$: C, 79.83; H, 8.21; O, 11.96. Found: C, 79.64; H, 8.29; O, 11.72.

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A Convenient Procedure for the Preparation of Ethoxyacetylene and Ethoxyethynyl Carbinols

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The use of ethoxyacetylene in organic synthesis is well-known.[2a,b] The condensation of ketones or aldehydes with the anion of ethoxyacetylene yields carbinols, which may be converted to α,β-unsaturated esters, aldehydes, or carboxylic acids.[2c-f] Ethoxyacetylene undergoes cycloaddition reactions with ketenes to form cyclobutenone ethers.[2g-i] It has also been used as a coupling reagent in the synthesis of peptides[2j] and acid anhydrides.[2b]

Although ethoxyacetylene is commercially available, it is expensive and generally requires distillation prior to use. The standard methods for the preparation of ethoxyacetylene involve the reaction of chloroacetaldehyde diethyl acetal[3,4] or β-bromovinyl ethers[5] with either sodium amide or lithium amide in liquid ammonia. These methods are time consuming and inconvenient, and the isolated ethoxyacetylene often contains significant amounts of ethanol.[6] Furthermore, it is not practical to synthesize carbinols by the direct reaction of ketones or aldehydes with sodium ethoxyacetylide prepared by these methods.[7]

Scheme I

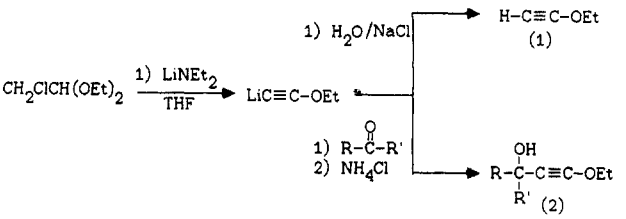

Table I

entry	carbonyl compd	2 isolated yield, %	2 lit. yield, % (ref)
a	acetone	95	60 (10)
b	propionaldehyde	91	47 (11)
c	methyl vinyl ketone	72	30 (10)
d	benzaldehyde	71	72 (11)
e	cyclohexanone	81	67 (7)
f	cholestan-3-one	75	~90[a] (12)

[a] Crude yield.

We now wish to report that treatment of chloroacetaldehyde diethyl acetal with 3 equiv of lithium diethylamide in THF at 0 °C affords lithium ethoxyacetylide, which may be conveniently converted to either ethoxyacetylene or ethoxyethynyl carbinols (Scheme I). Ethoxyacetylene is obtained by evaporation of the volatiles (THF, diethylamine, and hexanes) at reduced pressure, quenching the resulting lithium salts with saturated aqueous sodium chloride, and extraction of the aqueous solution with xylenes. Ethoxyacetylene (bp 48–50 °C) is distilled from the xylenes as a colorless liquid free of ethanol in 70% yield. If the presence of small amounts of ethanol and water in the ethoxyacetylene is acceptable, an alternate workup may be employed. The ethoxyacetylene is distilled directly from the aqueous solution through a short Vigreux column (bp 40–50 °C) into a −78 °C trap, and the ethoxyacetylene is decanted from the water that freezes at the bottom of the trap.

Ethoxyethynyl carbinols may be prepared directly from the lithium ethoxyacetylide generated in THF at 0 °C by reaction with aldehydes or ketones (Table I). If necessary, the ethoxyethynyl carbinol may be purified by Kugelrohr distillation or flash chromatography. Valuable or high-boiling carbonyl compounds may be used as the limiting reagent.[8]

The application of this modified procedure in the synthesis of ethoxyacetylene or ethoxyethynyl carbinols involves considerably less time than the previously reported procedures and does not require liquid ammonia solvent, and the reactions proceed cleanly and efficiently.

Experimental Section

Boiling points are uncorrected. ^1H NMR spectra were obtained on a Varian EM-360 (60 MHz), a Varian CFT-20 (80 MHz), or a Varian VXR-300 (300 MHz) instrument. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane, and cou-

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(6) NMR integration shows that ethoxyacetylene thus obtained contains 15–20 mol % ethanol.

(7) Braude, E. A.; Wheeler, O. H. *J. Chem. Soc.* **1955**, 320.

(8) Using nonvolatile aldehydes or ketones as the limiting reagent greatly simplifies isolation of the carbinol.

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